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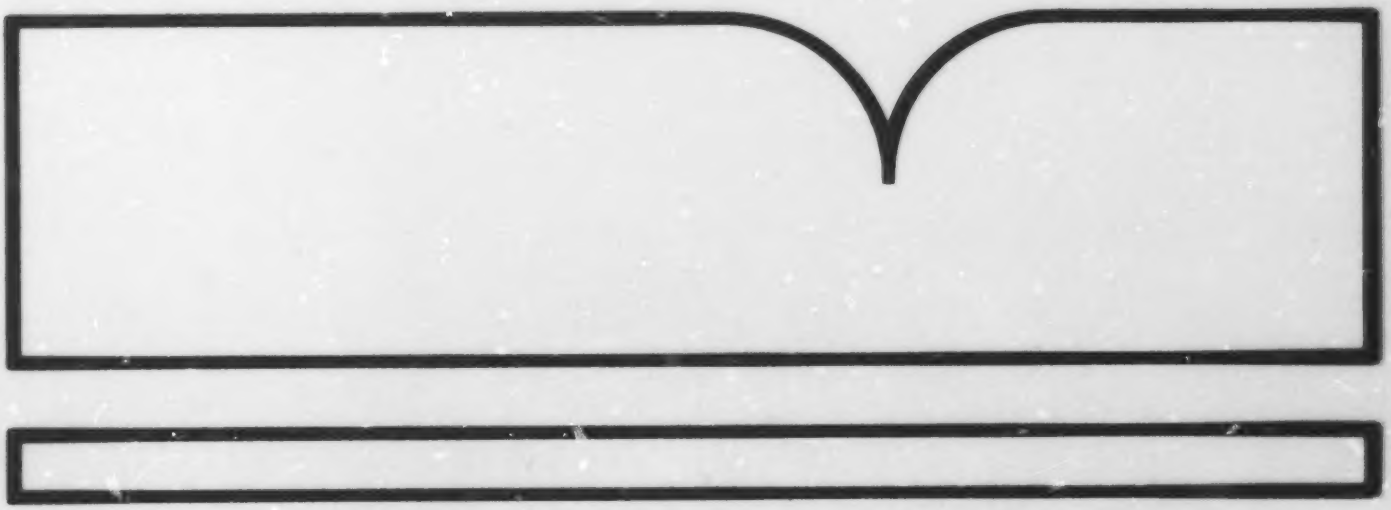

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16. ABSTRACT

The survival curves and the incidence of spontaneous diseases were studied in a population of SENCAR mice, a stock derived by a selected breeding protocol for enhanced susceptibility to chemical carcinogenesis in the skin. SENCAR mice proved to be as long-lived as other mouse strains or stocks, including one of their parental lines, Charles River CD-1. The most frequently occurring neoplasias in SENCAR mice were lymphoma, myeloid leukemia and reticulum cell sarcoma. Other frequently occurring neoplastic diseases included lung adenomas and carcinoma and mammary gland carcinoma. However, the incidence of these tumors was not higher than the incidence in CD-1 mice or other mouse strains or stocks. A variety of non-neoplastic diseases, both inflammatory and degenerative, were also observed in old mice. The most common were liver, spleen and kidney amyloidosis, pyelonephritis and papillary necrosis. These data indicate that selective breeding for susceptibility to chemical carcinogenesis has not produced a concomitant increase in the incidence of spontaneous neoplastic and non-neoplastic disease.

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JOURNAL ARTICLE

Survival curves and incidence of neoplastic and non-neoplastic disease in SENCAR mice

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The survival curves and the incidence of spontaneous diseases were studied in a population of SENCAR mice, a stock derived by a selected breeding protocol for enhanced susceptibility to chemical carcinogenesis in the skin. SENCAR mice proved to be as long-lived as other mouse strains or stocks, including one of their parental lines, Charles River CD-1. The most frequently occurring neoplasias in SENCAR mice were lymphoma, myeloid leukemia and reticulum cell sarcoma. Other frequently occurring neoplastic diseases included lung adenomas and carcinoma and mammary gland carcinoma. However, the incidence of these tumors was not higher than the incidence in CD-1 mice or other mouse strains or stocks. A variety of non-neoplastic diseases, both inflammatory and degenerative, were also observed in old mice. The most common were liver, spleen and kidney amyloidosis, pyelonephritis and papillary necrosis. These data indicate that selective breeding for susceptibility to chemical carcinogenesis has not produced a concomitant increase in the incidence of spontaneous neoplastic and non-neoplastic disease.

Introduction

The SENCAR mouse was developed by a selective breeding protocol for enhanced susceptibility to the initiation-promotion protocol for skin carcinogenesis (1,2). The cellular and molecular basis for the susceptibility of the SENCAR mouse is still not completely elucidated. Studies from several laboratories have shown that carcinogen metabolism capabilities in the SENCAR mouse are similar to those in other stocks and strains of mice (2,3), but tissue cultures derived from SENCAR mice show greater binding of epidermal growth factor (4) and a higher frequency of spontaneous, differentiation-resistant foci (5). From these experiments it has been suggested that normal SENCAR mouse skin may contain an inherent population of initiated cells.

Since the use of SENCAR mice has become very common for the study of chemical carcinogenesis, it is considered very important to know the background of spontaneous tumors and non-neoplastic diseases of this stock of mice. This information is necessary for planning and interpreting long-term experiments and also for understanding the mechanism of enhanced susceptibility of SENCAR mice to chemical carcinogenesis.

We report herein the survival curves and the neoplastic and non-neoplastic lesions of a population of 500 SENCAR mice maintained under conventional housing conditions.

Materials and methods

SENCAR mice were originally obtained from Dr. R.K.Boutwell of Madison, WI and kept as an outbred stock by continuous random mating. Periodical serological tests for common laboratory animal pathogens were performed to maintain adequate sanitary conditions. Two hundred and seventy-five females and 225 males bred at the Oak Ridge National Laboratory were housed 10 per cage, sexes separated, and given food and water *ad libitum*. The mice were observed until natural death occurred.

Cages were checked daily for dead or moribund animals. The latter were sacrificed; a complete necropsy was performed on every dead mouse. Brain, sternum, thoracic and abdominal organs and all the abnormal tissues were fixed in Zenker-Formol Fixative and embedded in paraffin. Microscopic study was carried out on 5–7 μm sections stained with hematoxilin-eosin.

Records were maintained on the date of birth, date of death, and gross and microscopic necropsy findings for each mouse. Those mice too autolyzed for pathologic examination were excluded from the disease-analysis group but were used for life-span curves.

Results and Discussion

The survival curves of 275 female and 225 male SENCAR mice are given in Figure 1. The respective average values, 50% survival and maximum survival, are represented in Table I. In this experiment, ~50% of the mice survived 2 years under normal housing conditions. Long-lived mice survived up to 3 years. In Table I we have also included data on other mice stocks or strains obtained from the literature. From these data it can be observed

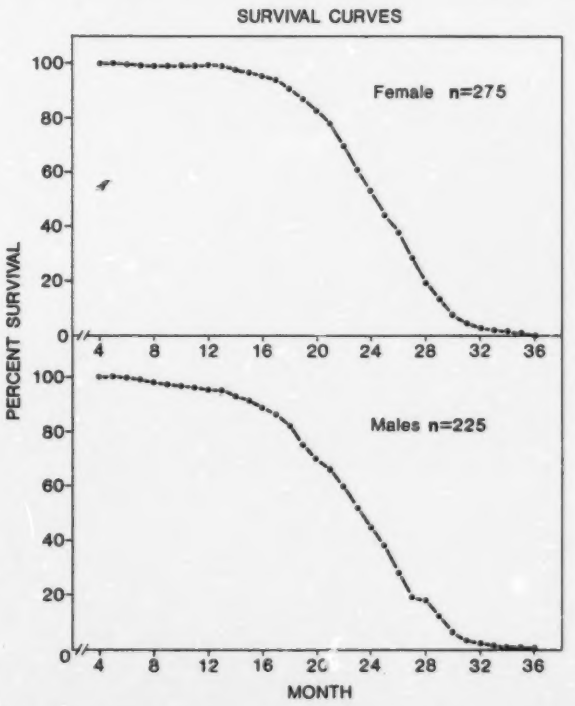

Fig. 1. Survival curves of male and female SENCAR mice.

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Table I. Survival data for SENCAR and other mouse strains and stocks

	Males			Females			Reference
	n[a]	50%[b]	Long-lived mice[c]	n[a]	50%[b]	Long-lived mice[c]	
SENCAR	225	23	36	275	24	36	This study
CBA/BrARij	179	28.8	36.2	240	20.5	40.2	(6)
RFM/Uhij	326	19.8	30.5	270	19.8	31.4	(6)
C57BL/Kalwrij	22	24.0	30.9	179	22.2	30	(6)
NZB/lac	153	18	27.5	164	14.3	21.5	(6)
LP/J	77	24.6	32.6	51	23.4	29.2	(7)
129/J	54	28.9	35.4	95	25.5	34.0	(7)
DBA/2J	67	19.7	28.7	51	19.6	27.1	(7)
CBA/J	17	25.5	28.7	33	21.6	26.6	(7)
C57BL/10ScSn	39	28.5	37.9	35	23.9	32.4	(7)
C3H	29	25.7	36.1	–	–	–	(7)
C3H.K	55	23.9	30.1	–	–	–	(7)
CD-1HAM/ICR	150	16	–	150	18	–	(8)

[a]n = number of mice in each study.
[b]50% = age (in months) at which 50% of animals survived.
[c]Long-lived mice = age of oldest surviving animal.

Table II. Spontaneous tumors in SENCAR mice

	Females (223)			Males (127)		
	Number	Percent	Average age	Number	Percent	Average age
Lung						
Adenoma	19	8.5	27.8	8	6.2	26.3
Adenocarcinoma	13	5.8	25.4	19	14.9	24.8
Hematopoietic						
Lymphoma	32	14.3	24.2	14	11.0	20.3
Reticulum cell sarcoma[a]	26	11.6	24.3	11	8.6	23.6
Myeloid leukemia	9	4	23.8	3	2.3	21.6
Liver						
Hepatoma	2	0.9	25.5	16	12.5	26.4
Subcutaneous and mesodermal						
Fibrosarcoma	7	3.1	24.3	7	5.5	22.4
Osteosarcoma	2	0.9	24.5	2	1.5	22
Chondrosarcoma	1	0.4	29	0	0	–
Breast						
Adenocarcinoma	39	17.4	23.9	–	–	–
Adenoacanthoma	4	1.7	22.2	–	–	–
Fibroadenoma	3	1.3	27.6	–	–	–
Stomach						
Adenocarcinoma	2	0.9	24.3	0	0	–
Uterus						
Carcinoma	0	0	–	–	–	–
Leiomyoma	1	0.4	28	–	–	–
Sarcoma	10	4	26.3	–	–	–
Ovary						
Granulosa tumor	6	2.6	25.5	–	–	–
Adenocarcinoma	1	0.4	23	–	–	–
Kidney						
Adenoma	0	0	–	1	0.7	37
Adenocarcinoma	0	0	–	1	0.7	19
Ear						
Adenocarcinoma	1	0.4	31	0	0	–
Pituitary						
Adenoma	2	0.9	20	0	0	–
Adrenal gland						
Cortical adenoma	1	0.4	27	0	0	–
Pheochromocytoma	–	–	–	1	0.7	27
Skin						
Papilloma	1	0.4	–	0	0	–
Squamous cell carcinoma	0	0	–	4	3.1	19.7
Others						
Harderian gland	1	0.4	32	1	0.7	24
Perianal adenocarcinoma	1	0.4	31	–	–	–
Central nervous system soft tissue	–	–	–	1	0.7	8
Hemangiosarcoma	–	–	–	1	0.7	15

[a]90% of the tumors in this category were Type A (histiocytic sarcoma); the rest were Type B (mixed lymphoma).

Table III. Non-neoplastic lesions in SENCAR mice

Site	Lesion	Female (223)		Male (127)	
		Number	Percent	Number	Percent
Skin	Abscess	2	0.9	2	1.6
	Cyst	2	0.9	1	0.8
Lung	Pneumonia	5	2.2	8	6.4
	Congestion and edema	12	5.4	6	4.8
Spleen	Hyperplasia	14	6.2	5	3.9
	Amyloidosis	11	4.9	13	10.2
Lymph node	Hyperplasia	10	4.4	4	3.2
Heart	Endocarditis	3	1.3	2	1.6
	Myocarditis	0	0	1	0.8
Liver	Necrosis	6	2.6	3	2.4
	Inflammation	2	0.9	3	2.4
	Amyloidosis	14	6.2	13	10.2
	Cyst	2	0.9	0	0
	Fatty metamorphosis	1	0.4	0	0
Pancreas	Islet cell hyperplasia	4	1.8	0	0
Adrenal	Hyperplasia	1	0.4	0	0
	Necrosis	3	1.3	2	1.6
Stomach	Inflammation	2	0.9	0	0
Kidney	Inflammation	11	4.9	3	2.4
	Pyelonephritis	19	8.5	20	15.7
	Papillary necrosis	13	5.8	11	8.6
	Glomerulonephritis	2	0.9	2	1.6
	Hydronephrosis	2	0.9	2	1.6
	Nephrosclerosis	5	2.2	7	5.5
	Calcium deposits	3	1.3	3	2.4
	Tubular necrosis	0	0	1	0.8
Urinary bladder	Inflammation	1	0.4	1	0.8
Uterus	Cystic hyperplasia	33	14.7	–	–
	Cyst (hydrometra)	3	1.3	–	–
	Pyometra	4	1.8	–	–
Ovary	Cyst	58	26.0	–	–
Male genitals	Abscess	–	–	4	3.2
	Calcium deposits	–	–	2	1.6

that SENCAR mice are as long-lived as other strains or stocks, especially one of the parental lines, Charles River CD-1 (6–8). This is a primary indication that the selection for susceptibility to chemical carcinogenesis has not produced an increase in the incidence of early neoplastic lesions or other non-neoplastic lesions.

In Table II all the tumors found in the necropsy of 223 female and 127 male SENCAR mice are represented. Most common were neoplasias of the hematopoietic system (lymphoma, reticulum cell sarcoma and myeloid leukemia), with an incidence of 30% in females and 22% in males. Other frequently observed tumors were lung adenocarcinoma (14.9% in males and 5.8% in females) and, in the female, mammary adenocarcinoma (17.4%). These figures are considered to be within the range of normal incidence of spontaneous tumors in standard strains and stocks of mice (1–6). The incidence of tumors in SENCAR mice also falls in the reported range of incidence of tumors in the parental stock CD-1, which is considered to be 10 to 20 times less susceptible to chemically induced skin carcinogenesis than SENCAR (3–7).

Non-neoplastic disease of various types, including inflammatory, degenerative, and proliferative lesions, were also observed in the SENCAR mice (Table III). The kidney was the organ most frequently altered in both sexes. Most of the older mice presented some degree of perivascular mononuclear infiltration, and severe pyelonephritis was diagnosed in 8.5% of the females and 15.7% of the males. Some of these older animals also presented papillary necrosis and severe atrophy with nephrosclerosis.

Kidney alterations were frequently associated with amyloidosis in various organs, mainly the liver and spleen. In a few animals, amyloid deposits were present in almost every organ (including the heart, skin, pancreas and salivary glands) and was probably the cause of death. Another common non-neoplastic finding was secondary hyperplasia of the spleen and the lymph nodes, which usually occurred in animals bearing tumors or inflammatory diseases.

Female mice frequently showed changes related to reproductive senescence such as ovarian cysts, cystic hyperplasia of the uterus, and hydrometra. Conversely, alterations in the male reproductive organs were not usually observed and the lesions recorded there were limited to two cases of calcium deposits in the testes and four cases of multiple abscess in the male genital organs. All of these lesions have been previously described in several stocks or strains and are common findings in the necropsies of laboratory mice (6–12).

The survival curves and incidence of spontaneous tumors of SENCAR mice show that their behavior is similar to that of other more resistant strains and stocks of mice, especially the Charles River CD-1 (2). Unfortunately, we have not been able to find pathological records of the Rockland, from which the other parental line was derived (1).

The relatively low frequency of tumors in many areas, including the skin and other organs of similar embryological origin,

suggests that the susceptibility of the SENCAR mouse to chemical carcinogenesis is related to interaction of the carcinogens with the mouse tissues (through metabolism or adduct formation, repair, or promotion) rather than to any systematic alteration. Systemic alterations such as decreased immunosurveillance should result in a high incidence of spontaneous tumors. Our findings agree with the findings in a previous work by Yuspa *et al.* (13), which showed that SENCAR skin retained a high sensitivity to chemical carcinogens when grafted in nude hosts.

Since we have not found a higher incidence of spontaneous tumors in SENCAR mice in this study, and since previous studies from our and other laboratories have shown that the application of tumor promoters alone produces a very low incidence of papillomas in this stock and virtually no carcinomas (2,14), it is unlikely that the high sensitivity of these mice to chemical carcinogens is attributable to constitutively initiated cells.

In conclusion, the life span and the incidence of spontaneous tumors and non-neoplastic diseases of the SENCAR mouse is equivalent to those of the other established stocks and strains of mice that are 10 to 20 times more resistant to chemical carcinogens. The reason(s) for the difference in their skin sensitivity to chemical carcinogenesis remain uncertain.

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